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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/026,587	12/18/2001	Manoj Kumar	GC558D2	9560

5100 7590 06/03/2004

GENENCOR INTERNATIONAL, INC.
ATTENTION: LEGAL DEPARTMENT
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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/026,587	KUMAR, MANOJ	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-39 and 41-52* is/are pending in the application.

4a) Of the above claim(s) *41-43 and 47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-39,44-46 and 48-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12-18-01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 32-39, 41-52 are currently pending and are present for examination. Claims 32-39, 44-46, 48-52 are now under consideration. Claims 41-43, 47 remain withdrawn from consideration as being drawn to non-elected invention.

Election/Restrictions

Applicant's election of Group I, claims 32-39, 44-46 and new claims 48-52 in Paper filed on 3-22-04 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-39, 44-46, 48-52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 32-39, 44-46, 48-52 are directed to a method of making a recombinant yeast using polynucleotides encoding polypeptides with specific activities. Claims 32-39, 44-46, 48-52 are rejected under this section of 35 USC 112 because the claims are directed to a method of use of a genus of polynucleotides encoding polypeptides that have not been disclosed in the specification. No description has been provided of the polynucleotide sequence encoding polypeptide sequences encompassed by the claim, for example 2,5,-diketo-L-gluconic acid reductase or D-sorbitol dehydrogenase etc. No information, beyond the reference to the activity of the encoded polypeptides has been provided by applicants which would indicate that they had possession of the claimed genus of polynucleotides encoding said polypeptides. The specification does not contain any disclosure of the structure of all the polynucleotide sequences within the scope of the claimed genus. The genus of polynucleotides encoding said polypeptides claimed is a large variable genus which can have a wide variety of structures. Therefore many structurally unrelated polynucleotides are encompassed within the scope of these claims. The specification discloses only functional characteristics of the genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 32-38, 44-46, 48-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murakawa et al. (Agric. Biol. Chem., Vol 41(9):1799-1800), Hardy et al. (US 4,945, 052 issued Jul 31, 1990) and Anderson et al. (US 5,032,514, 7-16-1991). Claims 32-38, 44, 46, 48-52 in this instant application are drawn to a method of producing a recombinant yeast capable of utilizing a six carbon sugar to produce ascorbic acid or an ascorbic acid stereoisomer comprising the steps of obtaining a yeast capable of utilizing 2-keto-L-gulonic acid (KLG) as a carbon source to produce ASA and introducing at least either or both of a heterologous nucleic acid sequence capable of encoding an oxidative enzyme associated with the production of ascorbic acid or an ascorbic acid stereoisomer in said yeast and a heterologous nucleic acid sequence encoding a reducing enzyme such as 2-keto-D-gluconic acid dehydrogenase and 2,5 DGK reductase respectively, rendering the yeast capable of utilizing 2-keto-L-gulonic acid (2-KLG), an intermediate in the biosynthesis of ascorbic acid and finally bioconverting KLG to ascorbic acid, wherein said yeast is a member of Cryptococcaceae, belonging to genus *Candida* or *Cryptococcus* specifically *C.blankii* or *C.dimennae* .

Murakawa et al. teach the production of ascorbic acid from non-recombinant yeasts using wide variety of sugars including glucose. However, the yields appear to be low. Thus, it appears that it was well known in the art that 2,3-DKG occurs among yeasts and that they are capable of producing ascorbic acid.

Andersen et al. teach a metabolic pathway for engineering an increased production of ascorbic acid intermediates by using recombinant technology by transfer of genes responsible for

the bioconversion of a six carbon sugar such as glucose to 2-KLG which is next oxidized to ascorbic acid using the very same enzymes taught in this instant application. (See entire document, specifically, column 1, lines 55-69 and column 2, lines 61-66; column 3 lines 33-36, 43-48, 63-69; column 4, lines 26-32, 43-60; column 5 line 43; column 11, lines 15-43, column 13, lines 26-3637-65, column 18-19, example 4). However, the reference does not teach the utilization of yeasts for the fermentative method or the bioconversion method. The reference does teach that the recombinant technique can be used using any appropriate host cells (see column 7, lines 63-68 and column 8, lines 1-8).

Hardy et al. teach the production of vitamin C precursor, 2, 5-DKG, in genetically modified microorganisms including several bacteria, fungi and yeasts (see column 5, last para) by transforming yeast host cells using a vector expressing the enzyme required for converting 2,5DKG to 2-KLG. The reference teaches recombinant methods and suggests the use of a list of microorganisms and mammalian cells as host cells.

With the above references in hand, it would have been obvious to one skilled in the art at the time the invention was made to combine the teachings of Murakawa et al. with that of Andersen et al. or Hardy et al. to develop a method of producing a recombinant yeast such as a *Candida*, capable of utilizing 2KLG and convert it into ascorbic acid. Murakawa et al. teach that yeasts are capable of producing ascorbic acid. Hardy et al. teach the use of yeasts as host organisms. Because the production of ascorbic acid is low among yeasts, one skilled in the art would be motivated to combine the teachings of Murakawa et al. with that of the molecular biological techniques of Andersen et al. to develop yeasts capable of utilizing glucose more efficiently and produce ascorbic acid in large amounts such that ascorbic acid can be produced

on a commercial scale in a one pot synthesis. Furthermore, Andersen et al. reference also teach that one would be motivated to do this as there are several advantages of having a yeast, a well known industrial microorganism, capable of producing vitamin C, to produce large amounts of ascorbic acid which has a huge demand in food and pharmaceutical industry. One would have a reasonable expectation of success since Murakawa et al. demonstrate the production of vitamin C from yeasts which are well known as fermentation work horse and Andersen et al. provide the entire metabolic machinery and the genes and enzymes necessary for doing the same and Hardy et al. demonstrate that yeasts can be used as host cells to introduce vectors for vitamin C precursor enzymes.

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art to have performed the claimed invention.

Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Murakawa et al. (Agric. Biol. Chem., Vol 41(9):1799-1800), Hardy et al. (US 4,945, 052 issued Jul 31, 1990) and Anderson et al. (US 5,032,514, 7-16-1991) as applied to claims 32-38, 44-46, 48-52 above, and further in view of Saito et al. (Appl. Environ. Microbiol., 1997, Vol. 63(2):454-460). Claims 39 is drawn to a method of making a recombinant yeast specifically *C.blankii* or *C. dimennae* and wherein said six carbon sugar comprises sorbitol and wherein said yeast comprises at least one heterologous polynucleotide encoding a L-sorbose dehydrogenase rendering it able to produce ascorbic acid or an ascorbic acid stereoisomer comprising using sorbitol by expressing a heterologous gene for an oxidative and reductive enzyme such as L-sorbose dehydrogenase, to produce KLG from sorbitol.

The references of Murakawa et al., Hardy et al. and Anderson et al. have all been discussed above. Saito et al. disclose the cloning of the genes coding for L-sorbose dehydrogenase and also teach the use of a recombinant bacteria transformed with said gene capable of using sorbitol for production of KLG. However, the reference does not teach a recombinant yeast strain comprising the said genes.

Combining the above references it would have been obvious to one of ordinary skill in the art to develop a method of transforming a yeast cell with the sorbitol dehydrogenase activity taught by Saito et al. in order to obtain a recombinant yeast capable of using sorbitol to produce KLG and further convert the same to ascorbic acid. One of ordinary skill in the art would have bee motivated to do so in order to use a cheap carbon source, sorbitol, for production of ascorbic acid. One of ordinary skill in the art would have a reasonable expectation of success since all the references except for Saito et al. teach the making of a yeast or a recombinant yeast for ascorbic acid production and Saito et al. specifically teach the use of sorbitol dehydrogenase genes for achieving the same goal using a cheap carbon source.

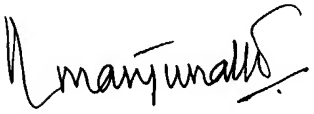
Therefore it would have been *prima facie* obvious to one of ordinary skill in the art to have performed the claimed invention.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the

examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 703-872-9306 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



Manjunath N. Rao
May 28, 2004